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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/750,101 | 05/01/97 | DOLLY J | ALRGN.054CP1 |

HM21/0323

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| EXAMINER | |
|---|---|
| MINNIFIELD,N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

**DATE MAILED:** 03/23/98

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/750,101 | Applicant(s) DOLLY ET AL |
|---|---|---|
| | Examiner N. M. MINNIFELD | Group Art Unit 1645 |

☒ Responsive to communication(s) filed on *12-30-97 Form PTOL 305 is attached.*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-4, 7, 8, and 15-32* is/are pending in the application.

Of the above, claim(s) *15-21 and 26-32* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☒ Claim(s) *1-4, 7, 8, and 22-25* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892 (7 sheets total)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

X PTOL-305

X CRF/Notice to Comply

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

**DETAILED ACTION**

1. EFFECTIVE FEBRUARY 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645. We are now in Technology Center 1600, Group 1640 and Art Unit 1645.

2. Applicants' amendments filed November 27, 1996 and May 22, 1997 are acknowledged and have been entered. Claims 1-4, 7, 8 and 20 have been amended. Claims 5, 6 and 9-14 have been canceled. New claims 21-32 have been added. Claims 1-4, 7, 8 and 15-32 are now pending in the present application.

3. It is noted that the Revocation of Prior Power of attorney filed December 30, 1997 has been entered and accepted; all future correspondence will be mailed to Mr. Carlos Fisher as requested. A copy of Form PTOL-305 is attached.

4. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claims 1-4, 7, 8 and 22-25, drawn to modified toxin (inactive toxin), pharmaceutical composition and method of treatment.

Group II, claims 15-21 and 26-32, drawn to modified toxin (active toxin), pharmaceutical composition and method of treatment.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature in Group I is the inactive Clostridial neurotoxin, whereas the special technical feature for Group II is the active Clostridial neurotoxin.

During a telephone conversation with Carlos Fisher on February 23, 1998 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-4, 7, 8 and 22-25. Affirmation of this election must be made by applicant in replying to this Office action. Claims 15-21 and 26-32 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

5. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y). The claim is vague and indefinite because it contains the use of an alternative expression wherein the limitation covers two different elements, i.e. "$His^{227}$" is not the same as "$Glu^{224}$". See MPEP 706.03(d), paragraph 5.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 102(b) as anticipated by Bizzini.

Bizzini discloses a composition that comprises tetanus toxin and is bound to a thiol group, and that this composition can be used to transport agents for medicine to the central nervous system (abstract; col. 2, l. 56-60). Bizzini discloses the use of fragments of the tetanus toxin that are atoxic (i.e. inactive) (col. 2, l. 36-45). Bizzini discloses that medicines can be transported into the nervous system via the medicine being bound to the thioliated polypeptide compound (tetanus toxin), employed as a transport agent (col. 6, l. 1-40; claims).

The prior art anticipates the claimed invention.

11. Claims 1, 2, 7, 24 and 25 are rejected under 35 U.S.C. 102(e) as anticipated by Mond et al.

Mond et al disclose a construct comprising two immunogenic carriers, and that such constructs are suitable for use in the diagnosis, treatment, and prevention of diseases (abstract). The prior art discloses a tetanus toxin coupled (i.e. attached) to a bioactive molecule (*H. influenzae* PRP) (col. 16-17). The prior art discloses the use of tetanus toxoid, therefore it is inactive (claims).

The prior art anticipates the claimed invention.

12. Claims 1, 2, 7, 8, and 22-24 are rejected under 35 U.S.C. 102(e) as anticipated by Johnson et al or Halpern.

Johnson et al disclose a composition comprising *C. botulinum* neurotoxin associated with non-toxic botulinum-derived proteins and pharmaceutically acceptable solutions for the purpose of use in a method to treat uncontrollable muscle spasms (abstract; col. 2, l. 42-67; claims).

Halpern discloses the tetanus toxoid conjugated to a carrier protein and that this composition is useful in methods of treating tetanus infection which has manifestations of neurological systems including muscle spasms (abstract; p. 1; p. 3; p. 8).

The prior art anticipates the claimed invention.

13. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bizzini taken with Fraenkel-Conrat et al.

Bizzini teaches a composition that comprises tetanus toxin and is bound to a thiol group, and that this composition can be used to transport agents for medicine to the central nervous system (abstract; col. 2, l. 56-60). Bizzini teaches the use of fragments of the tetanus toxin that are atoxic (i.e. inactive) (col. 2, l. 36-45). Bizzini teaches that medicines can be transported into the nervous system via the medicine being bound to the thioliated polypeptide compound (tetanus toxin), employed as a transport agent (col. 6, l. 1-40; claims). The prior art teaches the claimed invention except or the concept of amino acid modification of the neurotoxin. However, Fraenkel-Conrat et al teach amino acid substitution of the light chain of tetanus toxin. Fraenkel-Conrat et al also teach fusion (attachment) of another bioactive molecule. Fraenkel-Conrat et al teach that the mutant light chain of tetanus toxin was inactive. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the inactive and modified neurotoxin of Fraenkel-Conrat et al in a composition for the purpose of treating tetanus infection. Both references teach the concept of using inactive neurotoxins. The claimed invention id prima facie obvious in view of Bizzini taken with Fraenkel-Conrat et al, absent any convincing evidence to the contrary.

14. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant is given ONE MONTH, or THIRTY DAYS, whichever is longer, from the mailing date of this letter within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

15. No claims are allowed.

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula K. Hutzell, Ph.D., can be reached on (703) 308-4310. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield

March 15, 1998

NITA MINNIFIELD
PRIMARY EXAMINER

Application No.: 8/750101

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s)

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

**Applicant Must Provide:**

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

**PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE**